

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID: SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0
DICTIONARY FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter **HELP USAGETERMS** for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/reqprops.html>

=> E "RM2"/CN 25

E1	1	RM-ACID/CN
E2	1	RM189/CN
E3	0	--> RM2/CN
E4	1	RM38/CN
E5	1	RM60 HOMOPOLYMER/CN
E6	1	RM7/CN
E7	1	RM711/CN
E8	1	RM715/CN
E9	1	RM721/CN
E10	1	RM723/CN
E11	1	RM80/CN
E12	1	RM801FW/CN
E13	2	RMA 1/CN
E14	1	RMA 1 (FLUX)/CN
E15	1	RMA 1 (RUBBER)/CN
E16	1	RMA 101/CN
E17	1	RMA 150M/CN

E18	1	RMA 1X/CN
E19	1	RMA 2/CN
E20	1	RMA 300M/CN
E21	1	RMA 325/CN
E22	1	RMA 390DH3/CN
E23	1	RMA 4/CN
E24	1	RMA 400/CN
E25	1	RMA 450M/CN
 => E "RM-2"/CN 25		
E1	1	RM LUTE/CN
E2	1	RM PROTEIN (BACILLUS THURINGIENSIS ENTOMOCIDUS STRAIN LB1T-113
PLASMID PUIB1-1)/CN		
E3	0	--> RM-2/CN
E4	1	RM-ACID/CN
E5	1	RM189/CN
E6	1	RM38/CN
E7	1	RM60 HOMOPOLYMER/CN
E8	1	RM7/CN
E9	1	RM711/CN
E10	1	RM715/CN
E11	1	RM721/CN
E12	1	RM723/CN
E13	1	RM80/CN
E14	1	RM801FW/CN
E15	2	RMA 1/CN
E16	1	RMA 1 (FLUX) /CN
E17	1	RMA 1 (RUBBER) /CN
E18	1	RMA 101/CN
E19	1	RMA 150M/CN
E20	1	RMA 1X/CN
E21	1	RMA 2/CN
E22	1	RMA 300M/CN
E23	1	RMA 325/CN
E24	1	RMA 390DH3/CN
E25	1	RMA 4/CN

=> file caplus		SINCE FILE	TOTAL
COST IN U.S. DOLLARS		ENTRY	SESSION
FULL ESTIMATED COST		0.44	0.65

FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006
 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
 PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
 COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 13 Jun 2006 VOL 144 ISS 25
 FILE LAST UPDATED: 12 Jun 2006 (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
 They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> s us 20050221397/pn
L1 1 US 20050221397/PN
(US2005221397/PN)

=> sel rn
E1 THROUGH E1 ASSIGNED

=> file reg
COST IN U.S. DOLLARS SINCE FILE TOTAL
FULL ESTIMATED COST ENTRY SESSION
2.49 3.14

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0
DICTIONARY FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> s el
L2 1 850223-38-0/BI
(850223-38-0/RN)

=> d ibib
'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual
fields or predefined formats. The predefined substance formats
are: (RN = CAS Registry Number)

```

REG      - RN
SAM      - Index Name, MF, and structure - no RN
FIDE     - All substance data, except sequence data
IDE      - FIDE, but only 50 names
SQIDE    - IDE, plus sequence data
SQIDE3   - Same as SQIDE, but 3-letter amino acid codes are used
SQD      - Protein sequence data, includes RN
SQD3     - Same as SQD, but 3-letter amino acid codes are used
SQN      - Protein sequence name information, includes RN

CALC     - Table of calculated properties
EPROP    - Table of experimental properties
PROP     - EPROP and CALC

```

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

```

ABS  -- Abstract
APPS -- Application and Priority Information
BIB   -- CA Accession Number, plus Bibliographic Data
CAN   -- CA Accession Number
CBIB  -- CA Accession Number, plus Bibliographic Data (compressed)
IND   -- Index Data
IPC   -- International Patent Classification
PAT5  -- PI, SO
STD   -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB ----- AN, plus Bibliographic Data (original)
OIBIB ----- OBIB, indented with text labels

SBIB ----- BIB, no citations
SIBIB ----- IBIB, no citations

```

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.

The MAX format is the same as ALL.

The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

```

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

```

=> d 1

```

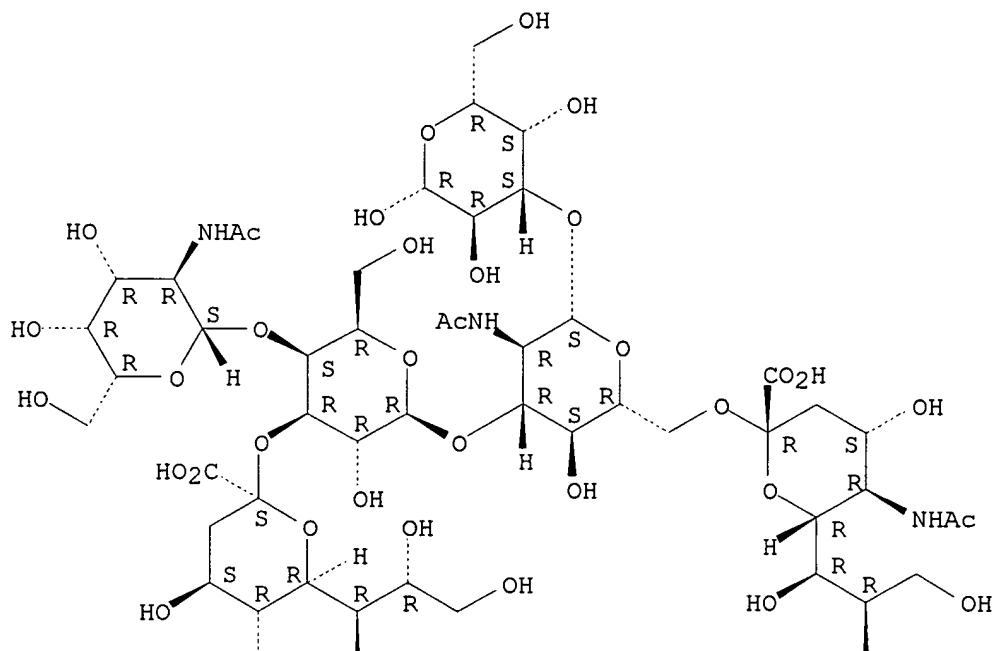
L2      ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN      850223-38-0  REGISTRY
ED      Entered STN: 11 May 2005
CN      β-D-Galactopyranose, O-2-(acetylamino)-2-deoxy-β-D-
          galactopyranosyl-(1→4)-O-[N-acetyl-α-neuraminosyl-
          (2→3)]-O-β-D-galactopyranosyl-(1→3)-O-[N-acetyl-α-
          neuraminosyl-(2→6)]-O-2-(acetylamino)-2-deoxy-β-D-
          glucopyranosyl-(1→3) - (9CI)  (CA INDEX NAME)
FS      STEREOSEARCH
MF      C50 H82 N4 O37
SR      CA

```

LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

||
NHAc ||
 OH

||
OH

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus
COST IN U.S. DOLLARS
FULL ESTIMATED COST

SINCE FILE ENTRY	TOTAL SESSION
2.34	5.48

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing

of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 13 Jun 2006 VOL 144 ISS 25
FILE LAST UPDATED: 12 Jun 2006 (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> d his

(FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006)

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006
E "RM2"/CN 25
E "RM-2"/CN 25

FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006
L1 1 S US 20050221397/PN
SEL RN

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006
L2 1 S E1

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006

=> s 12
L3 2 L2

=> d ibib 1-2

L3 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1078089 CAPLUS
DOCUMENT NUMBER: 143:344596
TITLE: Rm2 antigen (beta1,4-galnac-disialyl-lc4) as prostate cancer-associated antigen
INVENTOR(S): Saito, Seiichi
PATENT ASSIGNEE(S): Northern Advancement Center for Science & Technology, S. Korea
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005221397	A1	20051006	US 2004-812357	20040330
WO 2005098434	A2	20051020	WO 2005-US10221	20050325
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2004-812357	A 20040330

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:373084 CAPLUS
DOCUMENT NUMBER: 142:408646
TITLE: RM2 antigen (β 1,4-GalNAc-disialyl-Lc4) as a new marker for prostate cancer
AUTHOR(S): Saito, Seiichi; Egawa, Shin; Endoh, Mareyuki; Ueno, Seiji; Ito, Akihiro; Numahata, Kenji; Satoh, Makoto; Kuwao, Sadahito; Baba, Shiro; Hakomori, Senitiroh; Arai, Yoichi
CORPORATE SOURCE: Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Japan
SOURCE: International Journal of Cancer (2005), 115(1), 105-113
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file pctfull			
COST IN U.S. DOLLARS		SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST		3.20	8.68

FILE 'PCTFULL' ENTERED AT 14:39:42 ON 13 JUN 2006
COPYRIGHT (C) 2006 Univentio

FILE LAST UPDATED: 13 JUN 2006 <20060613/UP>
MOST RECENT UPDATE WEEK: 200623 <200623/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN THIS FILE.
SEE
<http://www.stn-international.de/stndatabases/details/ ipc-reform.html> >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
(last updated April 10, 2006) <<<

=> s RM2
L4 397 RM2

=> s antibod?
L5 88553 ANTIBOD?

=> s 15 and 14
L6 95 L5 AND L4

=> s cancer? or tumor? or neoplas?
78950 CANCER?
65926 TUMOR?
22900 NEOPLAS?
L7 98312 CANCER? OR TUMOR? OR NEOPLAS?

=> s 16 and 17
L8 67 L6 AND L7

=> s prostate and 18
24530 PROSTATE
421 PROSTATES

24544 PROSTATE
(PROSTATE OR PROSTATES)
L9 23 PROSTATE AND L8

=> s 19 not py>2002
408573 PY>2002
L10 8 L9 NOT PY>2002

=> d ibib 1-8

L10 ANSWER 1 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2002056022 PCTFULL ED 20020725 EW 200229
TITLE (ENGLISH): DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR
TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND
METHODS FOR TREATMENT OF CANCER
TITLE (FRENCH): MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE
MEDICAMENTS POUR L'INHIBITION DE LA
TUMORIGENÈSE, ET COMPOSITIONS ET PROCÉDÉS POUR
LE TRAITEMENT DU CANCER
INVENTOR(S): BAMDAD, Cynthia, C., 142 Church Street, Newton, MA
02458, US;
BAMDAD, R., Shoshana, 142 Church Street, Newton, MA
02458, US
PATENT ASSIGNEE(S): MINERVA BIOTECHNOLOGIES CORPORATION, 142 Church Street,
Newton, MA 02458, US [US, US]
AGENT: POMIANEK, Michael, J.S., Wolf, Greenfield & Sacks, P.C.,
600 Atlantic Avenue, Boston, MA 02210\$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
-----	-----	-----
WO 2002056022	A2	20020718

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (ARIPO): AM AZ BY KG KZ MD RU TJ TM
RW (EAPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2001-US44782 A 20011127
PRIORITY INFO.: US 2000-60/253,361 20001127
US 2000-60/255,370 20001213
US 2000-60/256,027 20001215
US 2000-60/258,157 20001222
US 2001-60/259,615 20010103
US 2001-60/260,186 20010105
US 2001-60/266,169 20010202
US 2001-60/266,929 20010206
US 2001-60/278,093 20010323
US 2001-60/289,444 20010507
US 2001-60/294,887 20010531
US 2001-60/298,272 20010614

L10 ANSWER 2 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001042786 PCTFULL ED 20020827
TITLE (ENGLISH): SYSTEM FOR CELL BASED SCREENING : CELL SPREADING
TITLE (FRENCH): SYSTEME DE CRIBLAGE A BASE DE CELLULES
INVENTOR(S): SAMMAK, Paul;

PATENT ASSIGNEE(S): DUENSING, Thomas, D.;
 RUBIN, Richard
 CELLOMICS, INC.;
 SAMMAK, Paul;
 DUENSING, Thomas, D.;
 RUBIN, Richard
 Patent

DOCUMENT TYPE:
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001042786	A2	20010614

DESIGNATED STATES
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE
 DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE
 KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX
 NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
 UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG
 ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI
 FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA
 GN GW ML MR NE SN TD TG
 WO 2000-US33308 A 20001208
 US 1999-60/170,087 19991209

APPLICATION INFO.:
 PRIORITY INFO.:

L10 ANSWER 3 OF 8
 ACCESSION NUMBER: PCTFULL COPYRIGHT 2006 Univentio on STN
 2001000247 PCTFULL ED 20020828
 TITLE (ENGLISH): PEPTIDE-LIPID CONJUGATES, LIPOSOMES AND LIPOSOMAL DRUG
 DELIVERY
 TITLE (FRENCH): CONJUGUES PEPTIDES-LIPIDES, LIPOSOMES ET APPOINT DE
 MEDICAMENTS LIPOSOMIQUES
 INVENTOR(S): MEERS, Paul;
 PAK, Charles;
 ALI, Shaukat;
 JANOFF, Andrew;
 FRANKLIN, J., Craig;
 ERUKULLA, Ravi;
 CABRAL-LILLY, Donna;
 AHL, Patrick
 THE LIPOSOME COMPANY, INC.
 Patent

PATENT ASSIGNEE(S):
 DOCUMENT TYPE:
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001000247	A1	20010104

DESIGNATED STATES
 W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
 DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
 JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
 MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
 TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ
 TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK
 ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM
 GA GN GW ML MR NE SN TD TG
 WO 2000-US16248 A 20000613
 US 1999-09/343,650 19990629

APPLICATION INFO.:
 PRIORITY INFO.:

L10 ANSWER 4 OF 8
 ACCESSION NUMBER: PCTFULL COPYRIGHT 2006 Univentio on STN
 2000072686 PCTFULL ED 20020515
 TITLE (ENGLISH): REGULATION OF SYSTEMIC IMMUNE RESPONSES UTILIZING
 CYTOKINES AND ANTIGENS
 TITLE (FRENCH): REGULATION DE LA REPONSE IMMUNITAIRE SYSTEMIQUE A
 L'AIDE DE CYTOKINES ET D'ANTIGENES
 INVENTOR(S): HARDY, Steve;
 DRANOFF, GlennRP : NAKAMURA, Dean
 CELL GENESYS, INC.

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER KIND DATE

WO 2000072686 A1 20001207

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ
TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK
ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM
GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2000-US15190 A 20000602

PRIORITY INFO.:

US 1999-09/324,707 19990602

L10 ANSWER 5 OF 8

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2006 Univentio on STN
2000057899 PCTFULL ED 20020515

TITLE (ENGLISH):

THROMBOSPONDIN-2 AND USES THEREOF

TITLE (FRENCH):

LA THROMBOSPONDINE-2 ET SES UTILISATIONS

INVENTOR(S):

DETMAR, Michael;

STREIT, Michael

PATENT ASSIGNEE(S):

THE GENERAL HOSPITAL CORPORATION;

DETMAR, Michael;

STREIT, Michael

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER KIND DATE

WO 2000057899 A1 20001005

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ
UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES
FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA
GN GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2000-US7835 A 20000324

PRIORITY INFO.:

US 1999-60/127,221 19990331

L10 ANSWER 6 OF 8

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2006 Univentio on STN

2000029433 PCTFULL ED 20020515

TITLE (ENGLISH):

12-25-KDA BACTERIAL PROTEINS AND THEIR 116-58 KDA

POLYMERS FOR USE E.G. IN ANTI-TUMOR VACCINES

TITLE (FRENCH):

PRODUIT

INVENTOR(S):

KISLITCHKINE, Nikolay

PATENT ASSIGNEE(S):

TOLIN AS;

JONES, Elizabeth, Louise;

KISLITCHKINE, Nikolay

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER KIND DATE

WO 2000029433 A2 20000525

DESIGNATED STATES

W:

AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE
DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE
KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX

NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW
AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW
ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-GB3852 A 19991118
PRIORITY INFO.: RU 1998-98120511 19981118
GB 1999-9908663.9 19990415

L10 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997033908 PCTFULL ED 20020514
TITLE (ENGLISH): LYTIC PEPTIDES
TITLE (FRENCH): PEPTIDES LYTIQUES
INVENTOR(S): RIVETT, Donald, Edward;
HUDSON, Peter, John;
WERKMEISTER, Jerome, Anthony
PATENT ASSIGNEE(S): COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH
ORGANISATION;
RIVETT, Donald, Edward;
HUDSON, Peter, John;
WERKMEISTER, Jerome, Anthony
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9733908	A1	19970918

DESIGNATED STATES
W:
AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG
SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ
UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
MR NE SN TD TG
APPLICATION INFO.: WO 1997-AU160 A 19970313
PRIORITY INFO.: AU 1996-PN 8614 19960313

L10 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1995019169 PCTFULL ED 20020514
TITLE (ENGLISH): TREATMENT OF PLATELET DERIVED GROWTH FACTOR RELATED
DISORDERS SUCH AS CANCERS USING INHIBITORS OF
PLATELET DERIVED GROWTH RECEPTOR
TITLE (FRENCH): TRAITEMENT DE TROUBLES LIES AU FACTEUR MITOGENIQUE
PLAQUETTAIRE TELS QUE LES CANCER, UTILISANT
DES INHIBITEURS DU RECEPTEUR DE FACTEUR MITOGENIQUE
PLAQUETTAIRE
INVENTOR(S): HIRTH, Klaus, Peter;
SCHWARTZ, Donna, Pruess;
MANN, Elaine;
SHAWVER, Laura, Kay;
KERI, Gyorgy;
SZEKELY, Istvan;
BAJOR, Tamas;
HAIMICHAEL, Janis;
ORFI, Laszlo;
LEVITZKI, Alex;
GAZIT, Aviv;
ULLRICH, Axel;
LAMMERS, Reiner;
KABBINAVAR, Fairooz, F.;
SLAMON, Dennis, J.;
TANG, Cho, Peng
PATENT ASSIGNEE(S): SUGEN, INC.;

BIOSIGNAL LTD.;
VISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW
UNIVERSITY OF JERUSALEM;
MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER
WISSENSCHAFTEN E.V.;
REGENTS OF THE UNIVERSITY OF CALIFORNIA

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9519169	A2	19950720

DESIGNATED STATES

W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE
HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL
NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN KE MW SD
SZ AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF
BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1995-US363 A 19950106

PRIORITY INFO.: US 1994-8/179,570 19940107

=> d kwic 1

L10 ANSWER 1 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR
TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR
TREATMENT OF CANCER

TIFR MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE MEDICAMENTS POUR
L'INHIBITION DE LA TUMORIGENÈSE, ET COMPOSITIONS ET PROCÉDÉS
POUR LE TRAITEMENT DU CANCER

ABEN . . . a series of compositions, methods, kits, articles and species
associated primarily with the diagnosis and/or treatment of cell
proliferation, specifically cancer. Cell proliferation
associated with aberrant expression of MUC1 is particularly focused
upon. Mechanisms associated with MUC1 cell proliferation are discussed.

ABFR . . . de procédés, de trousse, d'articles et d'espèces associées
principalement au diagnostic et/ou au traitement de la prolifération
cellulaire, notamment du cancer. L'invention concerne en
particulier la prolifération cellulaire associée à l'expression
aberrante de MUC1, ainsi que des mécanismes associés à la. . .

DETD DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR
TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR
TREATMENT OF CANCER
Related Applications
This non-provisional application claims the benefit under Title 35,
U.S.C.

Field of the Invention

The invention relates to assays using shed cell surface receptor
interchain binding
regions and cleavage products for cancer diagnosis, and for
the evaluation of cancer
treatment and using the portion of the receptor that remains on the cell
as a molecular
target for cancer therapeutics.

of the Invention

Many of the biomolecular interactions that promote tumorogenesis
involve cell
surface proteins that mediate both intra- and intercellular signaling.
Tumor markers are
proteins on the surface of a cell that are exclusively expressed,

over-expressed or show an altered expression pattern as a result of transformation to a neoplastic state. The surface concentration of certain tumor markers has been correlated to the progression of cancer. For example, the interaction between the cell surface receptor aVP3 and the cell adhesion molecule vitronectin has been implicated in angiogenesis. . . .

Integrins and cancer. Curr Opin Cell Biol, 1996, 8(5): 724-730; Vailhe B, Ronot X, Tracqui P, Usson Y, Tracqui L: In vitro angiogenesis is. . . .

Cell surface receptors, that have been linked to cancer, make up an important class of therapeutic targets. Many pharmaceutical companies are actively involved in screening drug libraries for compounds that bind to and block these cell surface receptors. For example, an important drug used to treat breast cancer is Herceptin (Pegram M, Lipton A, Hayes D, Webber B, Baselga J, Tripathy D, Baly D, Baughman S, Twaddell T, Glaspy J, Slamon D: Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p 1 8 5 Her2/neu monoclonal antibody plus cisplatin, in patients with Her2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment, J Clin Oncol, 1998, 16(8): 2659-2671). This drug binds to and blocks HER2/neu (Ross J, Fletcher J: review, The Her2/neu oncogene in breast cancer. . . .

for therapy. Stem Cells, 1998, 16(6): 413-428) which is a cell surface receptor that is over-expressed on 30% of breast tumors. . . .

myeloma cells and is induced by dexamethasone. Blood, 1999, 93(4): 1287-1298), is especially interesting since it is aberrantly expressed on many human tumors, including 80% of breast tumors, and on a significant percentage of prostate, lung, ovarian, colorectal and perhaps brain, cancers. . . .

epithelium, MUC 1 is clustered at, the apical border and is not expressed over other portions of the cell. However, in tumor cells, the receptor is homogeneously over-expressed over the entire cell surface (Kufe D., Inghirami G., Abe M., Hayes D, Justi-Wheeler H, Schlom J: Differential reactivity of a novel monoclonal antibody (DF3) with human malignant versus benign breast tumors. Hybridoma, 1984, 3. . . .

223-232), rather than just at the apical border. It is also known that women with breast

cancer have elevated levels of shed MUC 1 receptor in their blood stream. Extracellular portions of the MUC 1 receptor are cleaved. . . least one enzyme, and released into the blood stream. Levels of shed MUC 1 receptor in serum are measured to track breast cancer patients for recurrence. However, the

method is too variable and
insensitive to be used as a general diagnostic.

Until now, the mechanistic link between the MUC I receptor and tumorigenesis has not been understood. Attempts to correlate the number of repeat units, which varies from person to person, and susceptibility to cancer failed. Investigations of a possible connection, between glycosylation of the MUC1 receptor and cancer, produced conflicting results. Importantly, until now, a functional ligand(s) for the extracellular portion of the MUC 1 receptor has not been identified.

Absent an understanding of the mechanism of the MUC I receptor, and how it triggers tumorigenesis, it has not been possible to design or identify therapeutics that interfere with the disease-associated function of this receptor. Indeed, currently there. . .

The present invention describes discoveries that elucidate critical aspects of the mechanism by which WC I triggers cell proliferation and tumorigenesis. These discoveries provide novel molecular targets for drug screening assays which the inventors have used to identify compounds that inhibit the WC. . .

of the Invention

The present invention provides a variety of kits, methods, compositions, peptide species and articles associated with cell proliferation, specifically cancer. The invention involves primarily techniques and components for the diagnosis and treatment of cancer.

Another method of the invention involves treating a subject having cancer or 30 being at risk for developing cancer, the method comprises administering to the subject an agent that reduces cleavage of a cell surface receptor.

Another method of the invention for treating a subject having cancer or at risk for developing cancer comprises administering to the subject an agent that reduces cleavage of a cell surface receptor interchain binding region from the cell. .

comprises determining an amount of cleavage of a cell surface receptor interchain binding region from a cell surface, and evaluating indication of cancer or potential for cancer based upon the determining step.

determining a site of cleavage of a cell surface receptor in a sample from a subject, and evaluating an indication of cancer or potential for cancer based upon the determining step.

Another method of the invention involves treating a subject to reduce the risk of

or progression of cancer. The method comprises administering to a subject, who is known to be at risk for cancer or is diagnosed with cancer, an agent for inhibiting interaction of an activating ligand with a portion of a cell surface receptor that interacts with the activating. . .

Another method of the invention involves treating a subject to reduce the risk of or progression of cancer. The method comprises administering to a subject, who is known to be at risk of cancer or is diagnosed with cancer, an agent for preventing clustering of portions of cell surface receptors that interact with an activating ligand such as a growth factor. . .

Another method involves diagnosing a physiological state indicative of cancer or potential for cancer. The method comprises determining a specific cleavage site of MUC I distinguishable from a different cleavage state of MUC I.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC 1 . comprising administering to the subject etomoxir in an amount effective to reduce tumor growth.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising administering to the subject L-cc-methyl-dopa in an amount effective to reduce tumor growth.

Another method of the invention for treating a subject having cancer characterized by the aberrant expression of MUC I, comprises administering to the subject calcimycin in an amount effective to reduce tumor growth.

Another method for treating a subject having a cancer characterized by the aberrant expression of MUC 1, comprises administering to the subject butylindazole in an amount effective to reduce tumor growth.

imply a disease-related cleavage site on the MUCI receptor;

Fig. 4 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes the receptor, enhances cell proliferation in a manner typical of a growth factor/receptor - antibody interaction;

Fig. 5 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes

the receptor, dramatically enhances. . . . used to detect inhibitors of the MUC 1 -Ligand interaction;

Fig. 13 shows a histogram illustrating the selective inhibition of proliferation of tumor cells that aberrantly express the WC I receptor, in response to treatment with

compounds of the invention, and lack of an effect. . . . of the WC I receptor and a multimerizing ligand(s);

Fig. 15 shows a histogram illustrating the selective inhibition of proliferation of tumor

cells that aberrantly express the WC I receptor, in response to treatment with drugs that

specifically inhibit MUC1 positive cells;

Fig. 16 shows. . . . to treatment with drugs that non-specifically inhibit cell proliferation;

Fig. 17 shows a histogram illustrating that drugs that selectively inhibit proliferation of

tumor cells that aberrantly express the WC I receptor bind to the PSMGFR, while drugs

that non-selectively inhibit cell proliferation do not;

Fig. 18 is a graph showing that the inhibition of WC 1 -dependent cell proliferation

induced by an anti-tumor drug identified in accordance with the invention, is modulated

when a synthetic peptide, corresponding to the portion of MUC I that. . . .

a mechanism in which this portion is made accessible to the ligand upon MUC I cleavage at a site associated with tumorigenesis that causes release of the IBR from the cell.

shed, or cleaved. The cleaved IBR of interest is a disease-associated cleavage, i.e. that type of cleavage that can result in cancer.

ratio with the IBR and forms part of the portion of MUC I that is shed upon cleavage in healthy and tumorigenic cells.

type of interaction that occurs between pairs of molecules including proteins, nucleic acids, glycoproteins, carbohydrates, hormones and the like. Specific examples include antibody/antigen,

antibody/hapten, enzyme/substrate, enzyme/inhibitor, enzyme/cofactor, binding protein/substrate, carrier protein/substrate, lectin/carbohydrate, receptor/hormone, receptor/effector, complementary strands of nucleic acid, protein/nucleic acid repressor/inducer, ligand/cell surface receptor, virus/ligand, etc.

the host system includes a synthetic species such as a polymer, dendrimer, etc., or a naturally-occurring species, for example an IgM antibody, which is not simply naturally present in the host system but is added to the host system from a source external to. . . .

a dimer, a tetramer, a higher multimer, or a complex comprising a plurality of molecular species. In

the context of MUC I tumor cells, an activating ligand can be a species produced by the cells that interacts with the MGFRs on the surface of the WC 1 tumor cells in a manner that effects inductive multimerization.

A MUC I presenting cell refers to both non-cancerous and cancerous cells expressing MUC I and/or MGFRs on the surface. A WC I tumor cell or NWC 1 cancer cell or cancerous MUC1 cell refers to a cancerous tumor cell that aberrantly expresses MUC I and/or MGFR on its surface.

limited to, a binding species such as a peptide synthesized on a polystyrene bead, a binding species specifically biologically coupled to an antibody which is bound to a protein such as protein A, which is attached to a bead, a binding species that forms.

cover in this coritext, means that there is no portion of the surface or 3o region that directly contacts a protein, antibody, or other species that prevents complete, direct coverage with the SAM. Ie. in preferred embodiments the surface or region includes, across its. . .

The term cancer, as used herein, may include but is not limited to: biliary tract cancer; bladder cancer; brain cancer including glioblastomas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hernalogical neoplasms including acute lymphocytic and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratoma, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor. Preferred cancers are; breast, prostate, lung, ovarian, colorectal, and brain cancer.

The term cancer treatment as described herein, may include but is not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the aforementioned methods. . . .

Another treatment for cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary. . . .

An agent for prevention of cancer or tumorigenesis means any agent that counteracts any process associated with cancer or tumorigenesis described herein. For example, an agent that interacts with (e.g., binds to) MGFR thereby reducing or preventing interaction, with. . . .

in a cell-free assay containing the enzyme and WC I receptors, and the rate or position of cleavage measured by antibody probing, Polymerase Chain Reaction (PCR), or the like. Alternatively, without first identifying enzymes that affect WC I, agents are screened against cells. . . . present WC I, the supernatant removed, and the cell remain tested for accessibility of the MGFR portion, e.g. using a labeled antibody to the MGFR. Agents can be identified from commercially available sources such as molecular libraries, or rationally designed based on known agents. . . .

reduces cleavage of the WC I receptor at any location. Such an agent can be used to treat a subject having cancer or at risk for developing cancer because if cleavage is prevented, then the accessibility of the MGFR, a functional receptor associated with cancer, is reduced or prevented. Such agents can be selected by exposing cells to a candidate agent and determine, in the supernatant,

A subject, as used herein, refers to any mammal (preferably, a human), and preferably a mammal that may be susceptible to tumorigenesis or cancer associated with the aberrant expression of MUC I. Examples include a human, non-human primate, cow, horse, pig, sheep, goat, dog, or cat. . . .

The present invention involves, generally, novel molecular targets for drug screening, therapeutics and diagnostics related to cancers that are characterized by the aberrant expression of a class of cell surface receptors characterized by interchain binding regions. One such set of cancers are those characterized by the aberrant expression of MUC I. Much of the description of the invention herein involves. . . to identify other cell surface receptors that function by this or a similar mechanism, and to apply the invention to those cancers characterized by aberrant expression of receptors. The invention is based on a novel mechanism involving cell surface receptors that have regions that. . . .

and progressing away from the cell. In at least one U.S. provisional patent application (earlier application(s)) filed by the same inventors, entitled Tumor Markers and Drug Screening for Tumorigenesis Inhibition, relating to MUC I diagnostics and other techniques, at least one region of MUC I was defined differently. It is to. . .

Cleavage of MUC1 may occur at a site at or near the C-terminal boundary of the IBR in tumor or cancer cells (between the cell and the IBR), releasing the IBR from the cell. Alternatively, cleavage of MUC1 may occur within the IBR itself to cause sufficient disrupting of the IBRs such that the. . .

from interacting with the MGFR portion of the receptor, which is proximal to the cell relative to the IBR. In a cancerous or tumor cell, this reticulum may be lost, allowing ligand interaction with the MGFR.

proliferation; and (b) blocking the interaction of this portion of the WC I receptor (MGFR) with its ligand(s), blocks cell proliferation. When tumor cell lines, in which the WC I receptor is homogeneously expressed across the entire cell surface, are treated with an IgG antibody raised against the MGFR portion of the WC I receptor, the rate of cell proliferation is greatly enhanced, see Fig. 5. Since IgG antibodies are bivalent, i.e. one antibody simultaneously binds to two adjacent MGFR portions on the cell surface, these results demonstrate that the antibody acts as an activating ligand, mimicing the effect of a growth factor, which dimerizes MGFR portions, and thus triggers a cell. . . of the receptor with a monomeric composition, thus preventing inductive multimerization and subsequent signaling cascades. For example, a single chain, or monovalent, antibody raised against the MGFR portion of the MUC1 receptor would function as an effective anti-cancer therapeutic. Another therapeutic strategy is to block the activity of enzymes that modify the receptor, which may be required for some ligand. . .

histidine tag of the peptide, the beads were then incubated with lysates and supernatants from a variety of cell types, including cancer cell lines that overexpress MUC1. Enzyme inhibitors such as PMSF were added to some of the lysates and supernatants to circumvent problems. . .

containing some or all of these ligand species. In one aspect, the invention involves modification and use of the above species as anti-cancer agents.

a protein known as Metastasis Inhibition Factor NM23, which has been implicated in both the promotion and inhibition of metastasis of human

cancers. Whether the role of NM23 is a tumor suppressor or promoter may depend on the type of cancer. In ovarian, colon and neuroblastoma tumors, NM23 overexpression has been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian carcinoma, *Anticancer Res*, 1996; 16(3A): II 97-202). However, breast cancer studies indicate that reduced expression of NM23 correlates with poor prognosis (Mao H, Liu H, Fu X, Fang Z, Abrams J, Worsham MJ, Loss of NM23 expression predicts distal metastases and poorer survival for breast cancer, *Int J Oncol* 2001 Mar; 18(3):587-91).

NOT

added to lysate) corresponded to more than one protein species, including 14 3, which is a signaling protein implicated in many cancers, and cathepsin D, which is a protease and is also implicated in tumor progression. 14 3 exists as a dimer and can simultaneously bind to two, identical phospho-serine peptides. This protein has been shown to. . .

a high degree of homology to beta-lipotropin (Odell W, Wolfsen A, Bachelot I, and Hirose F, (1979) Ectopic production of lipotropin by cancer *The American Journal of Medicine* 66; pgs.

the position of enzyme cleavage is associated with receptor clustering, accessibility of adjacent portions of the receptor to putative ligands, and thus cancer. Agents that modulate the activity of this enzyme may be potent anti-cancer agents. Additionally, an early diagnostic test for

cancers that aberrantly express MUC 1 may be based on detecting the portion of MUC I that self-aggregates (113R) circulating in bodily. . . cell surface after the release of the portion that self-aggregates (IBR - some or all of the PSIBR sequence) may be potent anti-cancer drugs. In addition, agents that block binding of the natural ligand to the remaining portion after the release of the IBR, . . . biomolecules and to artificially cluster the MGFRs. Another alternative agent, which can be used to artificially cluster the MGFRs is an IgM antibody raised against the MGFR or PSMGFR. This artificially-induced clustering may serve to keep the cytoplasmic tails clustered to prevent interaction with intracellular. . .

One aspect of the invention involves a novel drug screening assays, that identify therapeutics that interfere with the proliferation of tumor cells that aberrantly express MUC 1. The drug screen makes use of the new molecular target for cancer that is

disclosed herein. Another aspect of the invention involves therapeutics identified by the drug screen. Yet another aspect of the invention involves methods for diagnosing MUC I+ cancers, which is based upon the mechanism elucidated by the inventors.

assay which can rapidly identify agents that interrupt the interaction between the MGFR and its ligand(s) and thus can be used as cancer therapeutics, (see Example 5a and Fig. 12 for details).

60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER.

Agents so identified may be potent anti-cancer agents either in monomeric form or as polymers or dendrimers. Drug libraries and peptide libraries can be screened for molecules that inhibit. . .

its ligands. These methods include but are not limited to phage display methods, yeast two-hybrid system, sandwich assays, surface plasmon resonance-based assays, antibody-based assays, peptide bead assays for testing with drug libraries, bead assays, GFP-reporter assays, and the like. Ligands to the MGFR portion.

used to block binding of the remaining extracellular portion of cleaved MUC I to its natural ligand, and can potentially inhibit cancer growth.

of the invention is a drug screening assay for identification of drugs that can be useful for prevention and/or treatment of cancer by altering the cleavage state of WC 1 receptors on cells. In such assays, described in more detail below, cultured cells are. . . and/or dosage or other conditions involving exposure to the drugs. These cells can be derived from a particular patient, or can be tumor-associated or non-tumor-associated cell lines. Customized therapeutic protocols can be determined for a particular patient in this manner. The invention involves, in one aspect, treating. . . below, shown to affect the cleavage state of WC I of the patient's cells in a manner that prevents, inhibits, or reverses cancer.

suspected that the incorrect cleavage of WC 1 on the surface of the cell causes the cascade leading to proliferation and tumorigenesis, it would be advantageous to test candidate drugs in a whole cell assay for their ability to affect enzyme cleavage or the. . .

Colloids bearing an antibody, natural ligand, or small molecule that binds to either the cleaved portion of WC I, or the remaining extracellular portion (plus.

contained within the shed fragment. The aggregation

potential of peptides released into the cell media is tested by adding colloids bearing an

antibody to a sequence distal from the self-aggregating portion, but not a repeat sequence. In this way, antibody-presenting colloids would attach to upstream regions of MUC1. If the self-aggregating region was also attached to the released fragment, then this would. . .

of these portions or other structural constraint that inhibits their association with factors that promote cell proliferation. Alternatively, IgM-type monoclonal or polyclonal antibodies raised against the MGFR or PSMGFR could be utilized. Each anti-MGFR IgM antibody could be able to aggregate ten MGFRs on the cell surface to form preventative clusters.

I receptor can similarly be modified with other therapeutic agents. In this way, such a therapeutic can be directed to the tumor cells. For example, an agent that binds to the MGFR region of the WC 1 receptor can be modified with a radioactive substance to destroy tumor cells that aberrantly express the WC 1 receptor. Other toxic substances, such as ricin, as well as other therapeutics, can be. . . that bind to the MGFR could be modified to present a imaging agent for use in diagnostic imaging of MUC 1+ tumors and metastases. Such ligands can also, alternatively, be modified to act as drugs that can be useful for prevention and/or treatment of cancer. In one embodiment, a ligand, which in its unmodified form binds to multiple MGFRs causing inductive multimerization, is modified to remove or. . .

The discoveries presented herein: (1) that the IBR of MUC 1 self-aggregates; (2) that an antibody that dimerizes adjacent MGFR portions of the MUC 1 receptor leads to proliferation of WC 1 presenting tumor cells; and (3) that proliferation of MUC 1 presenting tumor cells can be inhibited by treatment with agents that target the MGFR and block the MGFR against interaction with a ligand, . . . the cell that WC 1 remains clustered, and the MGFR is inaccessible to ligands such as growth factors, and in a tumor cell, MUC 1 cleavage occurs such that enough of the IBR is cleaved from the cell such that WC 1 does. . .

The above-mentioned mechanistic model predicts that in a subject with a WC 1 - dependent tumor or who is prone to developing such a tumor, the portion of the MUC 1 receptor that is shed will contain the IBR region of the receptor, leaving the MGFR portion. . .

The cleavage state will differ between a healthy cell and a cell with

tumor potential. The cleavage state determination can involve determining whether cleavage occurs in a manner such that the normal interaction between the IBRs. . . .

and/or a signaling entity. Generally, an assay as described in WO 00/43791 or WO 00/34783 can be used. In a specific example,

antibodies to a portion of MUC I that would remain fastened to the IBR if the IBR is cleaved from the cell, such as antibodies to the repeats domain, are fastened to colloids.

The discovery that tumor cells can be treated with an agent that binds to the MGFR of MUC 1, or a ligand of MGFR, in a manner that inhibits cell proliferation leads to the conclusion that, in a diseased cell (a cancerous cell or a cell with potential for becoming cancerous), cleavage of MUC I occurs in a manner that allows MGFR to interact with at least one ligand in a manner that promotes tumorigenesis or cancer.

separated from the cell. The amounts of various receptor regions may be determined with any type of binding assay, e.g. an antibody-binding assay. For example, antibodies that specifically bind to the constant region or the repeats may be attached to surfaces (e.g. magnetic beads) to preconcentrate shed MUC I receptors prior to determining levels of IBR present. Then, for example, after pre-concentration of circulating MUC I receptors, antibodies to the IBR and antibodies to the constant region can be allowed to bind to the cleaved receptors, and determination of the ratio of binding of these antibodies reveals the ratio of IBR present relative to constant region present in the cleaved receptors, which in turn reveals the amount. . . . IBR relative to constant region present) for detecting IBR at a cell surface is an indicator of the presence of a tumor or the potential for the development of a tumor. A ratio that approaches 1: 1 when detecting these regions in shed receptors is likewise an indicator of cancer potential. This determination can indicate potential for tumor formation, existence of a tumor, progression of tumorigenesis, etc., and can thereby serve as a diagnostic and/or a evaluator of treatment for tumorigenesis. Another diagnostic aspect of the invention involves. . . . assay or a colloid bead assay (See above discussion and Examples, below). Alternative techniques involve determining the presence of the IBR using antibody probing assays, hybridization, PCR Reverse Transcriptase PCR (rtPCR), Ligase Chain Reaction (LCR), cycling probe technology, etc. In a preferred embodiment of the. . . .

The determination, in a blood sample, of the amount of cleaved receptor carrying

IBR, either involving antibody binding ratios, colloid binding assays, or the like can be made on a bodily fluid sample, such as a blood sample and optionally compared with other samples (e.g. to monitor the subject's progression of tumorigenesis or progression for treatment of the same) and/or controls.

site can be studied without removal of the tissue from the subject). In either of these studies, a primary indicator of tumorigenesis or potential for tumorigenesis is the amount of MGFR at a cell surface accessible to interaction with external agents such as growth factors, etc. This determination can be made, for example, by determining the amount of an antibody to the MGFR region that binds to the sample, either using standard antibody binding study techniques, or by exposing the sample to colloids to which antibodies specific to the MGFR region have been immobilized and determining binding of the colloids to the samples using techniques described in International patent publication numbers WO 00/34783 and WO 00/43791, referenced above. In another technique (perhaps more suited for an excised sample), antibodies to the MGFR region and to the IBR can be exposed to the sample and a determination made of the ratio of binding of each to the sample. A healthy sample will exhibit little or no antibody binding to the MGFR region. A sample indicating tumorigenesis or potential for tumorigenesis will show a non-zero ratio of MGFR antibody binding to IBR antibody binding.

a cell surface (rather than the amount of IBR in a shed portion) in a sample from a subject to evaluate cancer, or the potential to develop cancer in a subject.

information as to whether the IBR remains on the cell surface, or was shed from the cell surface, giving indication of cancer or tumorigenesis or the potential for either, as discussed above. Determining the site of cleavage can be accomplished by using enzyme-amplification methods.

pre- and post-treatment levels of cleaved cell surface receptor IBR, or cell surface receptor IBR at the surface of a cell, in cancer cells or tissues may be used to diagnose cancer in a subject or assess the effectiveness of treatment in a cancer patient. In a preferred embodiment the cell surface receptor is MUC 1.

Comparison of the levels of the above-mentioned regions with levels from subjects known to be free of cancer may allow determination of the presence of cancer in the subject. An example, although not intended to be limiting, is that a determination of the presence of elevated levels of . . . in a sample from a subject,

when compared to a level determined in samples from control subjects, may suggest the presence of cancer in the subject with elevated levels. Such methods of comparing levels of cancer-associated markers between a sample from a subject and a control sample for diagnostic purposes would be understood by one of ordinary. . . .

Examples of such methods include Western blotting, ELISA, antibody precipitation, PCR, LCR, rtPCR, cycling probe technology, and colloidal assays as described in international patent application serial no. PCT/US00/01997, filed 01/25/00, entitled 5Rapid. . . .

aspect of the invention, the cleavage state of MUC I can be used to determine progression or regression of a subject's cancer over time. The cleavage state also can be used to assess treatment parameters including, but not limited to: dosage, method of administration,

1 5 Another aspect of the invention involves extremely early-stage cancer diagnosis.

This aspect involves identification of patients who may be at risk for developing tumor or cancer associated with abnormal cleavage of MUC L These patients may not have developed tumors, but may exhibit a cleavage state indicative of a condition that can lead to cancer. In some instances, the subjects will already be undergoing treatment for 20 cancer, while in other instances the subjects will be without present cancer treatment. A test for a genetic predisposition to cancers characterized by aberrant MUC 1 expression of the invention is based on detecting genetic alterations in the MUC I cleavage enzyme(s), over. . . .

The fact that elevated levels of cleaved MUC1 are found in the blood of cancer patients is the basis for a blood test for breast cancer, which is not described herein.

is the identification of compounds that directly bind to the PSMGFR portion of the receptor. Therefore, a sensitive method for diagnosing early tumors is to administer to the patient, compounds that bind to the PSMGFR region that have also been derivatized with contrast or imaging agents. These compounds will agglomerate onto tumors wherein this portion of the NWC I receptor is accessible.

one aspect of the invention is directed to methods for treating a subject diagnosed with or at risk of developing a cancer or tumor characterized by the aberrant expression of MUCL The treatments of the present invention involve the use of drugs or agents as described herein. That is, one aspect involves a series of

compositions useful for treatment of cancer or tumor characterized by the aberrant expression of MUC I, including these compositions packaged in kits including instructions for use of the composition for. . . a description of use of the composition for participation in any biological or chemical mechanism disclosed herein that is associated with cancer or tumor. The kit also can include instructions for use of a combination of two or more compositions of some embodiments of the invention.. . . via another known route of drug delivery. These and other embodiments of the invention can also involve promotion of the treatment of cancer or tumor according to any of the techniques and compositions and combinations of compositions described herein.

even though the patients exhibit indication for treatment of one of the compositions of the invention for a condition different from cancer or tumor, including conditions that can be unrelated to cell proliferation or conditions that can accompany cell proliferation, cancer, or tumor. That is, if a composition of the invention is known for treatment of a different condition, some embodiments of the present invention also involve use of that composition for treatments that accompany cell proliferation, cancer, or tumor disease where indicated. These and other embodiments of the invention can include such treatment where the dosage, delivery technique or vehicle, . . . timing of administration, or other factor differs from the use of the composition for treatment of the condition different from cell proliferation, cancer, or tumor. In another set of embodiments, treatment of cell proliferation, cancer, or tumor with compositions of the invention may occur under 5 conditions that are similar to or overlap the use of compositions of. . . the invention for treatment of a different condition, but the compositions of the invention are promoted for treatments that accompany cell proliferation, cancer, or tumor or includes instructions for treatments that accompany cell proliferation, cancer, or tumor as mentioned above. As used herein, promoted includes all methods of doing business including methods of education, hospital and other clinical instruction,. . . written, oral, and electronic communication of any form, associated with compositions of the invention in connection with treatments that accompany cell proliferation, cancer, or tumor. Instructions can and often do define a component of promotion, and typically involve written instructions on or associated with packaging of compositions. . .

Subjects for whom certain treatment methods of the invention (with specific compositions directed toward cell proliferation, cancer, or tumor) are not intended are those who are diagnosed with a condition which may already call for

treatment with the specific composition. Accordingly, one aspect of the invention involves treatment of cell proliferation, cancer, or tumor with a specific composition disclosed herein for that purpose, not in combination with another agent where the other agent has been taught previously for use in treatment of cell proliferation, cancer, or tumor itself. Another embodiment involves treatment of cell proliferation, cancer, or tumor with this specific composition alone, not in combination with any other active agent. Another embodiment involves treatment of cell proliferation, cancer, or tumor with this specific composition where the use of the composition in the treatment is specifically instructed (through, e.g.

written instructions that can accompany the composition) for the treatment of cell proliferation, cancer, or tumor. In a preferred embodiment of this aspect, the invention involves treatment of cell proliferation, cancer, or tumor with the specific composition where the use of the composition in the treatment is specifically instructed to affect a mechanism associated with cell proliferation, cancer, or tumor as disclosed herein.

treated with drug s useful according to I 9

certain methods of the invention, including patients who are not suffering from cell proliferation, cancer, or tumor and who may or may not be presently indicating susceptibility to cell proliferation, cancer, or tumor. In other words, the preventative treatment preferably is directed to patient populations that otherwise are free of disease symptoms that call for. . .

NS 1 619 and etomoxir interrupt the interaction of MGFR with its ligand(s) that otherwise would bind to MGFR and promote tumorigensis.

In this aspect, the invention involves treatment of subjects associated with tumor or cancer associated with aberrant expression of MUC1 with these agents or a combination.

interfering with the MGFR-ligand interaction. All of the compounds inhibited cell proliferation, but roughly half of the compounds were toxic to both tumor cells that presented the MUC I receptor as well as cells that did not present this receptor. As discussed herein, the. .

to the MGFR

1 5 portion will have little or no toxic effects. Fusaric acid, L-U.-methyl-dopa and etomoxir selectively inhibited proliferation of tumor cells presenting MUC I while leaving control cells unaffected, see Fig. 13.

treatment with fusaric acid, but where the call for treatment with fasaric acid did not specifically call for treatment directed toward tumors or cancers associated with the aberrant expression of WC I, particularly in the dosages or other specific protocols described previously in U.S. Patent No. 6,127,393. Specific diseases listed in U.S. Patent No. 6,127,393 include skin cancer, breast cancer, prostate cancer, cervical cancer, colon cancer, liver cancer and lung cancer. In one embodiment, the methods of the present invention involve treatment with fusaric acid in dosages lower than that described in U.S.. . .

to the subject any one of calcimycin, fusaric acid, L-cc-methyl-dopa, butylindazole, NS 1619 and etomoxir in an amount effective to lower the risk/prevent/reduce/inhibit tumors or cancer associated with aberrant expression of MUC 1.

the specific route of administration and like factors within the knowledge and expertise of the health practitioner. For example, in connection with tumor or cancer associated with aberrant expression of NWC1, an effective amount is that amount which prevents interaction of MGFR with its ligand that otherwise. . .

(for agents that act according to that mechanism) so as to slow or halt the development of or the progression of tumor or cancer associated with aberrant expression of MUC 1. It is preferred generally that a maximum dose be used, that is, the highest. . .

administer higher and more frequent doses of the agent to a subject for example during or immediately following an event associated with tumor or cancer, provided still that such doses achieve the medically desirable result. On the other hand, it may be desirable to administer lower doses. . .

As noted, different drugs act according to different mechanisms. Drugs according to one mechanism interfere with MGFR binding to a tumorigenesis-promoting ligand, and do so to a particular degree relative to natural conditions for the subject in the absence of the drug.. . .

routes are available. The particular mode selected will depend, of course, upon the particular combination of drugs selected, the severity of the cancer condition being treated, the condition of the patient, and the dosage required for therapeutic efficacy. The methods of this invention, generally. .

Parenteral routes include subcutaneous, intravenous, intramuscular, or infusion. Direct injection may be preferred for local delivery to the site of the cancer. Oral administration may be preferred for prophylactic treatment e.g., in a subject at risk of developing a cancer, because of the convenience to the patient as well as the dosing schedule.

(e.g. tissue), such as (e.g. the vascular cell wall), by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein.

Use of a long-term sustained release implant may be particularly suitable for treatment of established cancer conditions as well as subjects at risk of developing a cancer. Long-term release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. The implant may be positioned at the site of the tumor.

The therapeutic agent may be administered in alone or in combination with an anti-cancer drug. If the therapeutic agent is administered in combination the compounds may be administered by the same method, e.g. intravenous, oral, etc. or may be administered separately by different modes, e.g. therapeutic agent administered orally, anti-cancer drug administered intravenously, etc. In one embodiment of the invention the therapeutic agent and the anti-cancer drug are co-administered intravenously. In another embodiment the therapeutic agent and the anti-cancer drug are administered separately.

Anti-cancer drugs that can be co-administered with the compounds of the invention include, but are not limited to Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; . . .

HHHHHHGFLGLSNIKFRPGSVVQLTLAFRE (SEQ ID NO: 4)
Histidine-Tagged Repeat Motif 2 (His-RM2).

GFLGLSNIKFRPGSVVQLTLAFRE (SEQ ID NO: 8)
Repeat Motif 2 (RM2).

Histidine-tagged peptides were synthesized with the sequences shown in table 1 (the various regions of MUC 1). The lyophilized peptides were. . . 2. Row A contains the His-PSIBR (primary sequence interchain binding region) peptide; Row B contains the His-TR peptide; Row C contains the His-RM2 peptide; Row D contains the His-PSMGFR peptide. Column 1 contains the His-PSIBR peptide; Column 2 contains the

His-TR peptide; Column 3 contains the His-RM2 peptide; and Column 4 contains the His-PSMGFR peptide. The solutions were observed for a color change. A change in solution color from. . . sequence of the interchain binding region (PSIBR), self-aggregates in a high affinity interaction, suggesting a mechanism by which the MUC1 receptor confers tumorigenesis.

Example 1b: Relationship Between MUC1 Cleavage Site in Tumor Conditions and NWC I Interchain Bindin
This example investigates the ability of peptide sequences near the boundary between the MGFR and P SIBR. . . the MUC 1 receptor to participate in self-aggregation, and thereby elucidates a probable cleavage site of NWC I that is associated with tumorigenesis or cancer.

This strongly suggests that cleavage of the MUC I receptor in tumors or cancers associated with aberrant expression of MUC I occurs at or near the boundary between the PSMGFR and PSIBR sequences, since it is demonstrated herein that in tumor cells that overexpress MUC I, the MGFR is accessible by agents that reduce cell proliferation by inhibiting the interaction between MGFR and. . . otherwise would promote cell proliferation. This also strongly suggests that the IBR is shed in cleavage of MUC I receptor in tumor or cancer associated with aberrant expression of WC I, but is not shed in cleavage of MUC I when WC I is normally expressed. . . That is, that the cleavage site of MUC I is at or near the C-terminal boundary of the IBR in tumor or cancer cells and IBR at or near the N-terminal boundary of the IBR in healthy cells.

In the remaining examples, the mechanism described above for cancer associated with aberrant expression of MUC I, in which an activating ligand (which is a growth factor) binds to multiple MGFRs at. . . which causes proliferation (inductive multimerization), is confirmed. Briefly, the mechanism is confirmed by showing that exposure of cells to a bivalent antibody raised 20 against MGFR induces cell proliferation characterized by a growth/response curve typical of a growth factor/receptor - antibody response (Example 2, below); the activating ligand produced by MUC I -presenting cells binds multiple PSMGFRs, and the amount of activating ligand. . . each cell type is proportional to the amount of MUC I receptor produced by that cell type (Example 3a-b, below); MUC1 tumor cells produce a species that is a multimer (Example 4b, below); and drugs found to be specific for MUC I tumor cells (drugs that inhibit proliferation in MUC 1 tumor cells but not other cells) are shown to bind to MGFR at cells, while those that are not

specific (those that inhibit MUC I tumor cells and other cells) are toxic in that they bind to the multimeric ligand and thereby remove it from interaction with. . .

of the MGFR portion of the WC I receptor triggers enhanced Cell Proliferation Consistent with the Mechanism Presented for MUC I Tumor Cells

This example demonstrates the effect of dimerization on the MUC I receptor. In this example it is shown that exposure of cells to a bivalent antibody grown against the MGFR region of the MUC I receptor, at varying concentration, results in enhanced cell

proliferation (or lack thereof) consistent with the mechanism presented for MUC1 tumor

cells. A bivalent antibody was raised against PSMGFR (i.e., a single antibody having the ability to bind simultaneously to two MGFRs was produced). MUC I tumor cells

(T47Ds) were exposed to this antibody, and cell proliferation was studied as a function of concentration of the antibody. A growth/response curve typical of a growth

factor/receptor - antibody response was observed.

Specifically, at concentration low enough that only a small portion of the cells were exposed to the antibody, cell -

proliferation was low. At a concentration of antibody high enough that one antibody could bind adjacent MGFRs, cell proliferation was maximized. At a high excess of

antibody, each antibody bound only a single MGFR, rather than dimerizing adjacent MGFRs, and proliferation was reduced.

T47D (HTB- 1 3 3) cells, a human breast cancer cell line that overexpresses

MUC I, were cultured to 30% confluency. An antibody raised against the PSMGFR

portion of the WC I receptor, i.e. an antibody to the MGFR (Zymed, San Francisco,

California, USA), was added to cells at varying concentrations in a multi-well cell

culture plate. As a negative control, a second set of T47D cells was treated with an

irrelevant antibody (anti-streptavidin). Prior to adding antibody, cells were counted (at time zero). All experiments were performed in triplicate. Cells were allowed to grow in

a CO₂ incubator under. . . well) at 24 hours and again at 48 hours.

Results, see Fig. 4, show that in a concentration-dependent manner, addition of antibody caused enhanced cell proliferation

compared to the proliferation of the same cells treated with a control antibody. Figure 4

is a graph in which measured cell growth at 24 and 48 hours is plotted as a function of

anti-PSMGFR concentration. At the optimal antibody concentration, when presumably

one antibody binds bivalently to two MGFR portions of the WC I receptor, i.e.

In a similar experiment, a concentration of the anti-PSMGFR

antibody, identified to maximize cell proliferation, was added to a first group of T47D tumor cells, grown as described above. The same amount of the anti-PSMGFR antibody was added to a set of control cells, K293 cells. Figure 5 shows that the addition of the anti-PSMGFR antibody to MUC I tumor cells (T47D) enhanced proliferation by 180% 24 hours, but had no effect on the control cells. The growth of the T47D cells plateaued to saturation, for cells with added antibody, at 48 hours. Control cells never reached saturation within the time frame of the experiment and were at 70% confluency at. . .

Activating Ligand Produced by MUC1-Presenting Cells Binds Multiple PSMGFRs
In this example, it is demonstrated that the activating ligand that triggers MUC I tumor cell proliferation binds multiple PSMGFRs simultaneously. Colloid particles were produced that carry immobilized PSMGFRs, and suspensions of these colloids were exposed to lysate and supernatants of (1) MUC1 tumor cells, or (2) control cells. MUC I tumor cell lysates/supernatants caused the colloids to aggregate (suspension turns blue) because the activating ligand contained in them binds MGFRs on different. . .

Lysates and supernatants from four different tumor-associated cell lines (HTB- 1 3 3 (also called T47D), CRL- 1 500, CRL 1504 and CRL- 1 902; ATCC, American Type. . .

Rows E-H contained colloid particles carrying a random sequence peptide. Columns 2, 5, 8, and I I contained lysates from a tumor cell line that overexpresses NWC1 (HTB-133). Columns 3, 6, 9, and 12 contained lysates from a

tumor cell line that does not express WC 1 (CRL- 1 902). Columns 1, 4, 7, and 1 0 contain lysates from a tumor cell line that expresses, but does not overexpress, NWC I (CRL- 1 504). Columns 1-3: NTA concentration on colloid: 20 micromolar;. . .

absence (Fig. 10) of the protease inhibitor PMSF (phenyl methyl sulfonyl fluoride). Lysates from T47D cells were used because this breast tumor cell line was known to overexpress MUC I; additionally, the inventors presented evidence herein (see Fig. 8A-D) that this cell line. . .

Culture Collection, Manasses, VA) and are all breast carcinoma cell lines. Some lines have been shown to express or over express the tumor marker receptor MUC 1, Her2/neu or the oncogenic enzyme cathepsin K.

from Mediatech supplemented with 1 mM sodium pyruvate, 10% FBS

Example 4b: Demonstration that the Ligand That Interacts with MUC 1 Cancer Cells is a Multimer
In this example, it is demonstrated that a ligand produced by MUC1 cancer cells that triggers cell proliferation in these cells is a multimer.

known as Metastasis Inhibition Factor NM23, which has been implicated in both the promotion and inhibition of metastasis of human 15 cancers. Whether the role of NM23 is a tumor suppressor or promoter may depend on the type of cancer. In ovarian, colon and neuroblastoma tumors, NM23 overexpression has been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian carcinoma, Anticancer Res, 1996; 16(3A): II 97-202). However, breast cancer studies indicate that reduced expression of NM23 correlates with poor prognosis (Mao H, Liu H, Fu X, Fang Z, Abrams J, Worsham MJ, Loss of nm23 expression predicts distal metastases and poorer survival for breast cancer, Int J Oncol 2001 Mar; 18(3):5 87-91).

from the protein gel band described in Figures 9 and 10 and that are derived from a protein implicated in many cancers called Metastasis Inhibition Factor NM23 are shown below in Table 4. NM23 exists as a hexamer and may recognize an unmodified form. . .

NOT added to lysate) corresponded to more than one protein species, including 14 3, which is a signaling protein implicated in many cancers, and cathepsin D, which is a protease and is also implicated in tumor progression. 14 3 exists as a dimer and can simultaneously bind to two, identical phospho-serine peptides. This would dimerize the MGFR portion. . .

QPGITFIAAK
3) human annexin V with Proline substitution by Threonine gi: 3212603
GLGTDEESILLLTSR
DLLDDLKSELTGK
SEIDLNFNIR
Examples 5a-d: Drug Studies Consistent with Mechanism Presented for MUC1 Cancer
In these examples, drugs that inhibit proliferation in MUC 1 tumor cells specifically were compared to drugs that inhibit proliferation in both MUC1 tumor cells and other cells. Drugs, both specific and non-specific, were identified by exposing them to PSMGFR-presenting colloids in the presence of WC 1 tumor cell lysates. Drugs were identified as those that prevented colloid-colloid interactions. Cell studies resulted in a separation of these drugs into two groups - a group specific for MUC 1 tumor cells

and a non-specific group. Non-specific drugs did not bind to PSMGFR, but are presumed to bind the activating ligand, and inhibit. . . somewhat toxic to both cell types, since they remove the activating ligand from interaction with the cells. Drugs specific for WC 1 tumor cells were found to bind to PSMGFR on beads, as demonstrated by HPLC analysis of the product of cleavage of PSMGFR. . .

of the MUC I Recepto
with its Activating Ligand(s)

The following is an example of a working drug screening assay to identify anti-

cancer agents. In this example, a histidine-tagged peptide derived from the portion of the MUC I receptor that remains attached to the. . .

The data below demonstrates the ability of anti-tumor drugs identified in accordance with the invention, specifically, calcimycin, fusaric acid, L-(X-methyl-dopa, butylindazole, NS 1 619 and etomoxir to inhibit proliferation of. . .

the interaction of the MGFR portion of the receptor with its activating ligands will block the proliferation of MUC I -presenting tumor cells. Therefore, drugs that were I 0 identified using the in vitro drug screening assay described in Example 5a were tested. . .

compared. As seen in Fig. 13, Etomoxir, L-alpha-methyl DOPA, and Fusaric acid selectively inhibited proliferation of the NWC I - expressing tumor cells over K293 negative control cells. The DMSO control cells (both T47D and K293) show that DMSO alone does not effect cell proliferation. Fig. 13 is a histogram illustrating the selective inhibition of proliferation of tumor cells that aberrantly express the MUC I receptor (T47D cell line), in response to treatment with compounds of the invention, and lack. . .

that were shown in the ftinctional cell proliferation assay (see Example 5b) to selectively inhibit the proliferation of WC I - presenting tumor cells by either directly binding to the MGFR portion or by acting on its modifying enzymes. Figure 15 is a bar graph that compares the percentage cell growth of WC 1 tumor cells (T47Ds) to a control cell line (K293 s), in response to treatment with novel drugs, (described in greater detail in. . .

provisional patent applications serial nos. 60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER). As is readily apparent, this group of drugs dramatically inhibited or completely prevented the proliferation of WC I -presenting tumor cells, while leaving the control cells, in most cases, unaffected.

provisional patent applications serial nos. 60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER) on cell growth for WC I -presenting cells (T47D) and a control cell line (K293). Notably, this group of drugs, which presumably. . .

6: Modulation of Inhibitory Effect of Etomoxir on Cell Proliferation Etomoxir, identified as a composition useful in treatment of NWC 1 -dependant

tumors in this invention, was shown to be specific for MGFR by modulating its effect on cell proliferation via competitive inhibition of. . .

Drugs That Affect MUC 1 Cleavage State

The release of the MUC 1 IBR can be correlated to the progression of cancer.

Tumor derived cells expressing a cell surface receptor of the type described above, are cultured and treated with a drug candidate. Following. . .

Colloids bearing a binding peptide e.g. an antibody against a constant region of the receptor, remote from the enzyme cleavage site (amino acid 425 -479 for MUC 1; 30. . .

to the diagnostics and screening assays of the invention, the invention relates to therapeutic methods for the treatment and prevention of cancer and related products. For instance, in one aspect the invention relates to a method for treating a subject having a cancer or at risk of developing cancer by administering to the subject an agent that reduces cleavage of a cell surface receptor IBR from a cell surface receptor.

CLMEN 10 A method of treating a subject to reduce the risk of or progression of cancer comprising: administering to a subject who is known to be at risk for cancer or is diagnosed with cancer an agent for inhibiting interaction of an activating ligand with a portion of a cell surface receptor that interacts with the. . .

16 The method of claim 10, wherein the cancers is selected from the group consisting of. breast, prostate, lung ovarian, colorectal, and brain cancer.

31 A method of treating a subject to reduce the risk or of progression of cancer comprising: administering to a subject who is known to be at risk of cancer or is diagnosed with cancer, an agent for preventative clustering of portions of cell surface receptors that interact with an activating ligand such as a growth factor. . .

36 The method of claim 3 1, wherein the cancer is selected from the group consisting of breast, prostate, lung ovarian, colorectal, and brain cancer.

84 A peptide species as in claim 68, wherein the fragment comprises at least a fragment of the sequence that corresponds. . . I that interacts with an activating ligand such as a growth factor to promote cell proliferation in association with MUC I -dependent tumorigenesis.

remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis such that a biomolecule that interacts with that portion of WC I that remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis interacts with the fragment.

in claim 109, wherein the synthetic drug is a derivative of etomoxir.

113. A method for treating a subject having a cancer characterized by the aberrant expression of MUC1, comprising: administering to the subject ftsaric acid in an amount effective to reduce tumor growth.

114. A method as in claim 1 13, wherein the subject is otherwise free of symptoms calling for treatment with calcimycin.

115. A. . . levels of shed interchain binding region are reduced relative to a control sample.

119. A method for treating a subject having a cancer characterized by the aberrant expression of WC I, comprising: administering to the subject etomoxir in an amount effective to reduce tumor growth.

120. A method as in claim 119, wherein the subject is otherwise free of symptoms

calling for treatment with etomoxin

121. A method. . . levels of shed interchain binding region are reduced relative to a control sample.

125. A method for treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising: administering to the subject L-(x-methyl-dopa in an amount effective to reduce tumor growth.

126. A method as in claim 125, wherein the subject is otherwise free of symptoms

calling for treatment with L-(x-methyl-dopa.

127. A. . . levels of shed interchain binding region are reduced relative to a control sample.

131. A method for treating a subject having a cancer characterized by the aberrant expression of WC 1, comprising: administering to the subject calcimycin in an amount effective to reduce tumor growth.

132. A method as in claim 13 1, wherein the subject is otherwise free of symptoms calling for treatment with calcimycin.

133. A. . . levels of shed interchain binding region are reduced relative to a control sample.

137. A method for treating a subject having a cancer characterized by the aberrant expression of WC I, comprising: administering to the subject butylindazole in an amount effective to reduce tumor growth.

138. A method as in claim 137, wherein the subject is otherwise free of symptoms calling for treatment with butylindazole.

. A method. . . levels of shed interchain binding region are reduced relative to a control sample.

143. A method for treating a subject having a cancer characterized by the aberrant expression of MUC 1, comprising: administering to the subject NS 1 619 in an amount effective to reduce tumor growth.

144. A method as in claim 143, wherein the subject is otherwise free of symptoms calling for treatment with NS 1619.

145. A. . . composition and the biomolecule; and determining disruption of the interaction by the candidate drug.

150. A method of treating a subject having cancer or at risk for developing cancer comprising: administering to the subject an agent that reduces cleavage of a cell surface receptor.

151. A method of treating a subject having cancer or at risk for developing cancer comprising: administering to the subject an agent that reduces cleavage of a cell surface receptor interchain binding region from the cell surface.

152. The. . . - corresponds to amino acids 1085 through 1109 of Genbank accession # PI5941, PID G547937).

156. The method of claim 150, wherein the cancer is selected from the group consisting of. breast, prostate, lung ovarian, colorectal, and brain cancer.

157. The method of claim 150, wherein the cancer is characterized by the aberrant expression of the WC I receptor.

158. A method comprising: determining an amount of cleavage of a cell surface receptor interchain binding region from a cell surface; and evaluating indication of cancer or potential for cancer based upon the determining step.

159. A method as in claim 158, wherein the cell surface receptor is MUCL

160. A method as in claim 158, comprising diagnosing cancer in a subject by determining an amount of shed cell surface receptor interchain binding region in a subject sample; and evaluating indication of cancer or potential for

cancer based upon the determining step.

161. A method as in claim 158, wherein the evaluating step comprises correlating the amount in a sample to an amount in a control as an indication of cancer or potential for cancer.

. A method as in claim 158, comprising: determining an amount of cell surface receptor interchain binding region at the surface of a cell from a subject; and evaluating indication of cancer or potential for cancer based upon the determining step.

163. The method of claim 158, wherein the interchain binding region comprises a contiguous amino acid sequence of . . . 160, wherein the sample is a proliferating cell line derived from a subject's cells.

. The method of claim 158, wherein the cancer is characterized by aberrant expression of MUC I.

171. The method of claim 158, wherein the amount of interchain binding region is determined. . . by a method selected from the group consisting of MALDI, western blotting, PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic cell sorting, fluorescence activated cell sorting, bead-based assays or an ELISA assay.

172. The method of claim 158, wherein the amount. . . method comprising: determining a site of cleavage of a cell surface receptor in a sample from a subject; and evaluating an indication of cancer or potential for cancer based upon the determining step.

176. The method of claim 175, wherein the cell surface receptor is MUC I.

177. The method of . . . blood.

180. The method of claim 175, wherein the sample is a tissue sample.

181. The method of claim 175, wherein the cancer is selected from the group consisting of breast, prostate, lung, ovarian, colorectal, and brain cancer.

182. A method as in claim 175, wherein the cancer is characterized by the aberrant expression of WC I.

183. The method of claim 175, wherein the site of cleavage is determined. . . a method selected from the group consisting of MALDI, western blotting, PCR, LCR, 15 rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic cell sorting, fluorescence activated cell sorting, bead-based assays or an ELISA assay.

184. The method of claim 175, wherein the . . . of claim 185, wherein the surface cell receptor is WC I.

187. A method of diagnosing a physiological state indicative of cancer or potential for

cancer, comprising determining a specific cleavage state of WC I distinguishable from

a different cleavage state of WC1.
. A method comprising:
determining a. . . 188, comprising comparing the first amount to the second amount as an indication of progression of and/or effectiveness of treatment for cancer.
190. A method as in claim 188, comprising comparing the first amount to the second amount as an indication for administration of an agent for prevention of cancer.
191. A method as in claim 188, wherein the subject is undergoing treatment for cancer, the method comprising comparing the first amount to the second amount as an indication of effectiveness of the treatment.
192. A method as in claim 188, wherein the cell surface receptor is WC1.
193. The method. . . method of claim 188, wherein the sample is a tissue sample.
I 0 199. The method of claim 188, wherein the cancer is selected from the group consisting of breast, prostate, lung, ovarian, colorectal, and brain cancer.
. by a method selected from the group consisting of MALDI, western blotting, PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic cell sorting, fluorescence activated cell sorting, bead-based assays or an ELISA assay.
202. The method of claim 188, wherein the amount. . .

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.60	23.28

STN INTERNATIONAL LOGOFF AT 14:43:49 ON 13 JUN 2006